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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,873	10/07/2003	Michael S. South	C-3203 / I	4357

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SENNIGER POWERS LEAVITT AND ROEDEL
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EXAMINER

RAO, DEEPAK R

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/680,873

Applicant(s)

SOUTH ET AL.

Examiner

Deepak Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-16, 20-24, 28-32 and 40-49 ~~is~~ are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12-16, 20-24, 28-32 and 40-49 ~~is~~ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application (PTO-152) |
| 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>030504 & 030405</u> . | 6) ☐ Other: _____ |

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DETAILED ACTION

Claims 12-16, 20-24, 28-32 and 40-49 are pending in this application.

Election/Restrictions

Applicant's election of the species disclosed in claim 16, page 222, lines 24-25 drawn to compounds of formula (as disclosed in claim 12) wherein R^2 is 3-aminophenyl; B is phenyl; A is CH_2 ; Y^0 is 4-amidinobenzyl and M is CCl is acknowledged. As the elected species was not found in the prior art, the election/restriction requirement is withdrawn and the entire scope of claims as presented in the instant application are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-16, 20-24, 28-32 and 40-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition or a method for treating thrombosis, does not reasonably provide enablement for a composition or a method for (a) inhibiting (i) thrombotic conditions (ii) formation of blood platelet aggregates and (iii) thrombus formation in blood; and (b) treating and/or preventing the conditions recited in claims 43-48. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The use disclosed in the specification is as anticoagulants for the treatment of thrombotic diseases requiring anticoagulant therapy. The specification provides that the compounds of the invention are capable of inhibiting activity of serine proteases related to the coagulation cascade, however, there are no test assays or data provided to demonstrate the activity of the compounds. A preferred IC₅₀ range is provided on page 176, however, there is no disclosure regarding how this data correlates with 'inhibiting thrombotic conditions' in general or 'treating or preventing' of various diseases of the instant claims. The data range provided for the compounds is insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the myriad of compounds embraced by the structural formula of the claims. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art (directed to factor Xa inhibitors or anticoagulants) for assuming the same. The area of receptor interactions is highly structure specific and unpredictable. The direction and extent of effects of anticoagulant interactions are not completely predictable. Furthermore, the results of the biological tests appear to be highly structure specific based on the range provided for the measured examples. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art.

The state of the art is not indicative of any anticoagulant agents for inhibiting thrombotic conditions in general. Further there are no known therapeutic or preventative agents for thrombotic conditions generally. Majerus et al. (cited in IDS) regarding Primary Prevention of

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Arterial Thromboembolism states that “the prophylactic use of aspirin in an apparently healthy population is not recommended at this time, unless there are risk factors for cardiovascular disease” (see page 1357). This clearly establishes that many factors need to be evaluated prior to administering anticoagulant or antiplatelet drug therapy in normal individuals. The examiner notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or references to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant preventive method. Prevention is seen to encompass administering the active agent to a baby or small child or healthy adult, and noting the fact that symptoms of thrombotic conditions such as coronary artery diseases, cerebrovascular diseases, etc. never manifest themselves. The state of the art reference, Handin (cited in IDS), states that “There are no clinical tests to screen patients suspected of having hypercoagulable or prethrombotic disorders”, thereby indicating the difficulty in identifying the ‘patients in need of’ the preventive treatment. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of prevention of the thrombotic conditions of the claims. Venous thromboembolism is often clinically silent. As a result, studies evaluating the efficacy of preventive measures generally screen patients who are asymptomatic. As widespread screening is not recommended in general practice, the incidence of venous thromboembolism in most studies appears higher than that encountered in clinical practice. The importance of clinically undetected venous thromboembolism is not fully understood. Also, the diagnosis of pulmonary embolism with or without pulmonary infarction is often difficult to establish unless special procedures are used.

Further, the scope of the method claims recites not only treatment but also “**prevention**” which is not adequately enabled solely based on the activity related to thrombin inhibition or anticoagulation provided in the specification. The claim language includes diseases that are known and those that are yet to be discovered, for which there is no enablement. Based on the IC₅₀ data (see specification page 24), the instant compounds are disclosed to be useful in the “prevention” of diseases such as venous thromboembolism, pulmonary embolism, etc., for which applicants provide no competent evidence. “To prevent” actually means *to anticipate or counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the “prevention” effect. The specification provides IC₅₀ values for the exemplified compound, however, it is inconceivable from this data as to how the claimed compounds can not only treat but also “prevent” a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening tests relied upon are recognized in the art as being reasonably predictive of success in any of the contemplated areas of ‘prevention’. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as ‘showing’ such utility, and not ‘warranting further study’). The evidence presented in this case does not show such utilities related to ‘prevention’, but only warrants further study.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that ‘a claimed invention must

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have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Rauch et al., (cited in IDS) wherein with regards to antithrombotic therapies, it is stated that "Current antithrombotic therapies available as long-term treatment for patients with cardiovascular disease are often not effective enough to prevent acute thrombotic events and deterioration of atherosclerosis". Also, Van Aken et al., (cited in IDS) with regards to therapeutic approach of thromboembolic disorders, expresses that 'thrombin inhibitors have limitations because their pharmacokinetics and anticoagulant effects are unpredictable'.

A patient's risk of venous thromboembolism varies depending on multiple factors including age, medical condition, type of surgery, duration of immobilization, and the presence of an underlying hypercoagulable state such as malignancy. Also, the site of cardiogenic thromboembolism is variable. Thromboembolism uncommonly occurs in the setting of a structurally normal or mildly abnormal heart. Effective recommendations for prevention of arterial thromboembolism have not been identified. Therefore, primary prevention of thromboembolism is basically a battle against the underlying cardiac disorder. No therapies have been identified that reverse or significantly retard the development of feline heart disease or its related pathologic or prothrombotic sequelae. Moreover, it is likely that multiple interactions are involved in thrombogenesis, including myocardial pathology and cardiac dysfunction, platelets, and other blood components and factors. Furthermore, there is no evidence of record which would enable the skilled artisan in the identification of the subjects that have the potential of needing such 'prevention of the diseases' encompassed by the instant claims. Regarding

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prevention of stroke, a state of the art reference, Hart et al., states that “Critical issues involving prevention of stroke for millions of persons with atrial fibrillation remain to be resolved by the next generation of studies. Reliable schemes to predict stroke risk must be refined and validated, and optimal antithrombotic prophylaxis awaits better understanding of the mechanisms linking predictors to stroke” (see pages 693-694).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Composition for inhibiting thrombotic conditions generally or therapeutic use of the composition in treating or preventing diseases that require thrombin inhibitory activity.

2) The state of the prior art: A very recent publication expressed that the pharmacokinetics and anticoagulant effects of thrombin inhibitors are unpredictable.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the ‘preventive’ effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

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4) The amount of direction or guidance present and 5) the presence or absence of working examples: The specification discloses that ‘the dosage regimen is selected depending on a variety of factors’ (see page 20, lines 20-26), however, the state of the art is that the effects of thrombin inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace not only treatment but also the **prevention** of diseases.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed methods.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards ‘preventing’ the variety of diseases of

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the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Note: The composition claims 12-16, 20-24 and 28-32 are included in the above rejection because they recite a particular intended use for the composition. See MPEP § 2164.01(c). When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 recites the limitation "a compound of any one of claims 12-16, 20-24 or 28-32" in lines 2-3. There is insufficient antecedent basis for this limitation in the base claims. The base claims 12-16, 20-24 and 28-32 are drawn to 'A composition' and not to "a compound".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

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Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 12-16, 20-24, 28-32 and 40-49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-29 of U.S. Patent No. 6,653,316. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly elected invention substantially overlaps the reference claims. The reference also teaches and claims compounds that are structurally analogous to the instantly claimed/elected compounds. One of ordinary skill in the art at the time of the invention would have been motivated to select any compounds of the reference genus, including the instantly claimed compound because he would have expected any of the compounds of the reference genus would have the same properties and therefore, the same use as taught for the reference genus as a whole.

2. Claims 12-16, 20-24, 28-32 and 40-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-53 of copending Application No. 10/680,723. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly elected invention substantially overlaps the reference claims. The reference also teaches and claims compounds

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that are structurally analogous to the instantly claimed/elected compounds. One of ordinary skill in the art at the time of the invention would have been motivated to select any compounds of the reference genus, including the instantly claimed compound because he would have expected any of the compounds of the reference genus would have the same properties and therefore, the same use as taught for the reference genus as a whole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Receipt is acknowledged of the Information Disclosure Statements filed on March 5, 2004 and March 4, 2005 and copies are enclosed herewith.

Conclusion

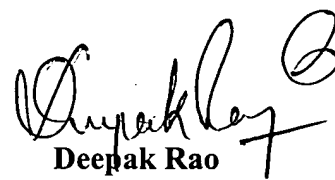
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

July 11, 2005